Diagnostic delay in narcolepsy type 1: combining the patients' and the doctors' perspectives

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Abstract: Narcolepsy type 1 is a neurological disorder characterized by a unique syndrome, including the pathognomonic symptom of cataplexy. The diagnosis can be confirmed by objective measures, such as typical findings in the multiple sleep latency test, reduced or undetectable levels of orexin (hypocretin) in the cerebrospinal fluid, and linkage to a specific HLA haplotype. Nevertheless, the mean time that elapses from symptom onset to the correct diagnosis ranges between 10 and 20 years, and the causes and correlates of this delay are poorly understood. Diagnostic delay was assessed on 52 well-defined patients with narcolepsy type 1, evaluating clinical, electrophysiological and neurochemical parameters and the results of a 41-item questionnaire developed to obtain the patients' perspective on various aspects of the diagnostic process. The mean time gap between disease onset and first medical consultation was 3.2 ± 5.1 years; the mean diagnostic delay was 8.9 ± 11.0 years. Prior to correct diagnosis, patients received a wide variety of misdiagnoses. The self-ratings of the patients revealed that the undiagnosed symptoms caused high levels of anxiety and unjustified criticism by family, friends and employers. Multiple regression analysis identified higher cerebrospinal fluid orexin levels (= 0.311, P = 0.01), and a longer interval between the onset of excessive daytime sleepiness and cataplexy (= 0.368, P = 0.002) as independent associates of longer diagnostic delay. The diagnostic delay decreased over the last decades (= -0.672, $P < 0.001$). In conclusion, delayed diagnosis of narcolepsy type 1 is very common, associated with many adverse consequences, and requires educational efforts to improve awareness on narcolepsy among healthcare providers and the general population.

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Diagnostic delay in narcolepsy type 1: Combining the patients' and the doctors' perspectives

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SUMMARY

Narcolepsy type 1 is a neurological disorder characterized by a unique syndrome, including the pathognomonic symptom of cataplexy. The diagnosis can be ~~convincingly~~ confirmed by objective measures such as typical findings in the multiple sleep latency test, reduced or undetectable levels of orexin (hypocretin) in the cerebrospinal fluid (CSF), and ~~a 95-100%~~ linkage to a specific HLA haplotype. Nevertheless, the mean time that elapses from symptom onset to the correct diagnosis ranges between 10-20y, and the causes and correlates of this delay are poorly understood. We assessed diagnostic delay ~~in~~ on 52 well-defined patients with narcolepsy type 1, evaluating clinical, electrophysiological and neurochemical parameters and the results of a 41-item questionnaire developed to obtain the patients' perspective on various aspects of the diagnostic process. Mean time gap between disease onset and first medical consultation was 3.2±5.1y; the mean diagnostic delay was 8.9±11.0y. Prior to correct diagnosis, patients received a wide variety of misdiagnoses. The self-ratings of the patients revealed that the undiagnosed symptoms caused high levels of anxiety and unjustified criticism by family, friends and employers. Multiple regression analysis identified higher CSF orexin levels (β=0.311, p=0.01), and longer interval between onset of excessive daytime sleepiness and cataplexy (β=0.368, p=0.002) as independent associates of longer diagnostic delay. The diagnostic delay decreased over the last decades (β=-0.672, p<0.001). In conclusion, delayed diagnosis of narcolepsy type 1 is very common, associated with many adverse consequences, and requires educational efforts to improve awareness on narcolepsy among health-care providers and the general population.

Key words: Narcolepsy / Cataplexy / Diagnostic delay / Orexin

INTRODUCTION

Narcolepsy type 1 is a neurological disorder characterized by excessive daytime sleepiness and cataplexy (Scammell, 2015). The narcoleptic pentad is complete, if the patient also presents hypnagogic or hypnopompic hallucinations, sleep paralysis and fragmented night-time sleep. Cataplexy, the ~~remarkable~~ sudden loss of muscle tone with emotions, is highly specific to narcolepsy type 1, and when familiar with this symptom, clinicians can easily ~~anticipate~~ make the correct diagnosis. The presence of typical findings on the multiple sleep latency test (MSLT), reduced or undetectable levels of orexin (hypocretin) in the cerebrospinal fluid (CSF), and a positive HLA-DQB1*06:02 haplotype usually allow an unequivocal diagnosis. In this regard, narcolepsy type 1 clearly differs from narcolepsy type 2, which remains a diagnostic challenge, as the symptoms are much less specific (no cataplexy) and the biomarkers~~, including CSF orexin levels and HLA haplotype,~~ are often not present (Baumann *et al.*, 2014).

Despite these reliable diagnostic criteria, the correct recognition of narcolepsy type 1 often occurs with a lengthy delay (Thorpy and Krieger, 2014). According to the few studies on this topic, the mean latency between disease onset and correct diagnosis varies between 8.7 years (Ingravallo *et al.*, 2012), 12 years (Frauscher *et al.*, 2013), 15 years (Morrish *et al.*, 2004), 16 years (Broughton *et al.*, 1997), and 19.3 years (Thorpy *et al.*, 1999). Up to half of all affected patients may actually never learn that they are suffering from narcolepsy (Scammell, 2015).

The failure of a correct and timely diagnosis is clearly a major issue, as narcolepsy is associated with deleterious life effects and high socio-economic burden (Black *et al.*, 2014; Broughton *et al.*, 1981; Ingravallo *et al.*, 2012), and because efficacious treatment options are now increasingly available. The reasons contributing to this long interval between disease onset and accurate diagnosis are poorly understood, and the above-mentioned studies have various methodological limitations, such as inclusion of both type 1 and 2 narcolepsy patients, lack of diagnostic confirmation by objective measures and reliance on medical records only.

The present single-center study aims at characterizing the diagnostic delay in well-defined patients with narcolepsy type 1, based on detailed clinical, electrophysiological and neurochemical parameters on the one hand and by using a 41-item questionnaire to obtain the patients' perspective on this issue on the other hand.

METHODS

This study was conducted at the Department of Neurology, University Hospital Zurich, Switzerland, between October 2014 and January 2016. The study protocol was approved by the Ethics Committee of the Canton of Zurich, specialized subcommittee for Psychiatry, Neurology, Neurosurgery (project number 2015-0165), and written informed consent was obtained by all patients at study inclusion.

Participants

We retrospectively identified 67 patients with narcolepsy type 1 with regular follow-ups at our sleep clinic since 2003. The diagnostic criteria for narcolepsy type 1 of the revised 3rd edition of the International Classification of Sleep Disorders (ICSD-3) were fulfilled in each patient. They all had persuasive cataplectic attacks. The diagnosis was confirmed by typical MSLT findings in 44 patients and reduced CSF orexin levels in 39 patients. HLA-genotyping was available in 42 patients. Two patients had to be excluded because they do not speak German, one patient had advanced Alzheimer's disease, one declined study participation, four patients were lost during follow-up, and seven patients did not return the questionnaire. Eventually, we included 52 patients (78%) in the study.

By performing a thorough chart review of these 52 patients, we retrieved data regarding year of onset of excessive daytime sleepiness and cataplexy, year of diagnosis and the respective ages of the patients. Demographical and clinical information included age,

sex, highest educational degree, current work capacity, and body-mass index. In-house MSLT data were available in 44 patients, and all had a mean sleep latency <8 minutes and ≥2 sleep onset REM periods. Measurement of CSF orexin levels was performed in 39 patients, using a radioimmunoassay (RIA) as previously described (Baumann *et al*., 2004); all patients had reduced CSF orexin levels. HLA-DQB1*06:02 was determined in 42 patients.

Questionnaire

Purely for the purpose of this study, we developed a questionnaire with 41 items regarding various aspects of the diagnostic process, the meaning of a correct diagnosis and the circumstances of delayed diagnosis. Most items describe situations or contain claims and the patients had to indicate on a visual analogue scale whether they agree or disagree, with 0 meaning maximal disagreement and 10 maximal agreement. Other items are questions and the patients had a choice between 3-5 different answers, with the possibility to mark multiple statements or to make additional comments. Seven question pairs inquired about disease-related consequences, comparing the situations before diagnosis and at the moment of study conduction.

Statistical analysis

Statistical analyses were performed using SPSS (version 22). Group data were described by means and standard deviations. For normally distributed data, we used Student's t-test, otherwise Mann–Whitney U-test was applied. Chi-square test was used for nominal data. We calculated Pearson's r for correlation analysis. We applied the paired samples t-test to compare the patients' ratings of their situations before and after diagnosis. To identify predictors of longer diagnostic delay, we performed stepwise multiple linear regression analysis with the following independent variables: year of disease onset, latency between onset of sleepiness and cataplexy, CSF orexin level, latency between symptom onset and first medical consultation, body mass index, Epworth Sleepiness Scale at

diagnosis, mean sleep latency on MSLT, age at diagnosis, education, number of symptoms at disease onset. Significance was accepted at $p<0.05$.

RESULTS

Table 1 provides a detailed overview on the patients' characteristics. In 37 patients (71%), the first manifestation of excessive daytime sleepiness and cataplexy occurred in the same year, but in the remaining 15 patients (29%) cataplexy occurred 3.8±4.3y later (range: 1-17y).

There was a time gap between disease onset and first medical consultation of 3.2±5.1y. This delay in seeking medical advice correlated with the overall diagnostic delay (r=0.576, $p<0.001$). Longer time gap to first medical consultation was associated with older age at diagnosis (r=0.342, $p=0.02$). Educational degree did not influence the time to first medical consultation (r=-0.215, $p=0.17$).

The diagnostic delay varied between 1 month and 43 years, with a mean of 8.9±11.0y and a median of 5.5y (**Fig. 1A**). Multiple linear regression analysis revealed higher CSF orexin levels (β=0.311, $p=0.01$) and longer interval between onset of excessive daytime sleepiness and cataplexy (β=0.368, $p=0.002$) as independent associates of a longer diagnostic delay. In addition, patients with longer diagnostic delay had a higher body mass index at the moment of diagnosis (r=0.274, $p=0.05$).

Over the last 50 years, the diagnostic delay (r=-0.737, $p<0.001$) and the latency from first symptom manifestation to first medical consultation (r=-0.568, $p<0.001$) became shorter (**Fig. 1B+C**). Multiple linear regression analysis identified earlier year of disease onset as strongest predictor of longer diagnostic delay (β=-0.672, $p<0.001$).

Patients rated the overall burden caused by the undiagnosed disease as 7.4±2.4 on the visual analogue scale. At the moment of study conduction, i.e. after diagnosis and

established treatment, the disease burden was reduced to 4.6±2.7 (p<0.001). As shown in **Fig. 2**, the undiagnosed disease had many adverse consequences in patients' life, with improvement of all aspects when narcolepsy was recognized as the responsible disorder. At disease onset, only 15 patients (29%) believed that the various narcoleptic symptoms belonged to one single disease; the majority did not spontaneously think about this question (60%) or thought that any symptom represents a different disease (11%). **Table 2** shows the various aspects related to the delayed recognition of the correct diagnosis. Most patients received one or more misdiagnoses (**Fig. 3**), together with many inappropriate diagnostic procedures and treatments.

The patients believe that the long interval that elapsed from disease onset to correct diagnosis has compromised many aspects of their life (**Fig. 4**). They emphasize that, in hindsight, many disadvantages would seem avoidable, if the correct diagnosis had been recognized earlier. When asked about the causes of the diagnostic delay, 64% of the patients blamed the treating physicians for insufficient knowledge on narcolepsy, 24% blamed themselves for not having sought medical advice earlier, and 12% regarded both delayed medical consultation and insufficient symptom recognition by their treating physicians as the main cause. Accordingly, a majority of the patients are convinced that a rapid diagnosis of narcolepsy requires improved knowledge among both physicians (69%) and the general population (77%).

DISCUSSION

This study confirms previous observations that there is a tendency over the last decades to diagnose narcolepsy with continuously shorter delay. Nevertheless, our findings reemphasize that people with narcolepsy are still sustaining many disadvantages because the correct diagnosis is recognized too late. There is considerable suffering not only because

efficacious treatment options are withheld, but also because patients are often criticized by their surroundings, who – like the physicians and the patients themselves – misinterpret their symptoms.

The diagnostic delay in our patient cohort is similar to the 8.7±8.5 years reported in 100 Italian patients with narcolepsy type 1 (Ingravallo *et al*., 2012), but shorter than in all other studies summarized in the review by Thorpy and Krieger (Thorpy and Krieger, 2014). Since the diagnostic delay seems to decrease in the last decades and years (Dauvilliers *et al*., 1998; Morrish *et al*., 2004), the shorter delay in our cohort and that of Ingravallo and colleagues may simply be explained because these are the most recent studies. This continuous reduction in diagnostic delay may reflect improved knowledge and growing awareness of narcolepsy among both health-care providers and the general population. Another similarity with the Italian study is that we only included patients with narcolepsy type 1. The absence of cataplexy was identified as an independent predictor of longer diagnostic delay among 219 narcolepsy patients living in the UK (Morrish *et al*., 2004), and our study corroborates the diagnostic importance of cataplexy by identifying longer interval between first manifestation of excessive daytime sleepiness and cataplexy as independent predictor of longer diagnostic delay. Moreover, higher CSF orexin levels were independently associated with longer diagnostic delay, possibly because a slower or incomplete loss of orexin-producing neurons leads to a more insidious emergence and milder severity of narcoleptic symptoms, in particular of cataplexy (Sturzenegger *et al*., 2004; Baumann *et al*., 2006; Valko *et al*., 2013).

Our patients waited on average more than 3 years until they eventually decided to seek medical advice, and roughly one third acknowledged that this hesitation was a main cause of the diagnostic delay. This indicates that a considerable diagnostic delay will persist even with optimal knowledge and awareness about narcolepsy among health-care providers. On the other hand, the majority of our patients had been referred to ≥3 physicians before correct diagnosis, suggesting indeed that many health-care providers are not familiar enough with the symptoms of narcolepsy. This ~~becomes~~ is also apparent when considering the long

list of misdiagnoses, and the inappropriate diagnostic procedures and treatments the patients ~~got~~ were prescribed. The most common misdiagnoses in our patient cohort were “iron deficiency”, “burnout” and “psychosomatic origin”, and a similarly wide variety of mental and neurological misdiagnoses has been reported by others (Campbell *et al*., 2011; Carter *et al*., 2014; Kauta and Marcus, 2012; Kryger *et al*., 2002; Macleod *et al*., 2005). Our observations are in keeping with the AWAKEN survey, where narcolepsy ranked lowest in the awareness of 1000 US adults compared to other chronic disorders, and physicians, including sleep medicine specialists, incompletely recognized all narcolepsy symptoms (Rosenberg and Kim, 2014).

Based on the questionnaire, receiving an accurate diagnosis appeared to improve many life aspects in our narcolepsy patients. While optimal treatment may in part account for this improvement, the domains with the most pronounced reductions after established diagnosis were anxiety and unjustified criticism by family, friends and employers. Thus, knowing the cause of their symptoms may alleviate the situation of narcolepsy patients beyond the benefits of pharmacological treatment.

The correlation between longer diagnostic delay and higher body mass index additionally highlights the importance of a timely diagnosis. Researchers recognized the involvement of orexin in feeding behavior and body weight regulation at the very moment of its discovery – *orexis* means “appetite” in Greek – and subsequent studies described increased body mass index and disturbed glucose and fat metabolism in patients with narcolepsy (Donjacour *et al*., 2014; Schuld *et al*., 2000). Moreover, treatment with sodium oxybate, currently the most commonly prescribed drug for narcolepsy patients in many sleep clinics, has been associated with weight loss (Husain *et al*., 2009), possibly because it stimulates lipolysis (Donjacour *et al*., 2014). Thus, early diagnosis and, hence, early treatment may reduce the patients’ risk of additional weight gain due to orexin deficiency.

Our study has limitations. First, the study design was retrospective, and the interval between the diagnostic process and the completion of the questionnaire differed significantly between patients. Therefore, some statements might be of uncertain reliability, as they

depend on the patients' memory. Second, our questionnaire is not validated, but was merely created for the purpose of this study. Third, the significant decrement in diagnostic delay over the last years may be artificially distorted, because the maximal delay is always limited by the interval between the year of disease onset and the moment of study conduction, thus becomes linearly shorter with every year. Nevertheless, the fact that we observed a similar decrement also for the interval to the first medical consultation, which naturally is much shorter than the diagnostic delay and therefore less prone to such distortion, indicates that the observed reduction over time can be regarded as real.

In conclusion, delayed diagnosis of narcolepsy type 1 remains a major challenge, is highly common and associated with negative repercussions on many life aspects in affected patients. The accurate registration of all narcolepsy cases in specific databases and the establishment of distributed expert networks such as the European Narcolepsy Network are a first step in the right direction (Khatami *et al.*, 2016). However, additional educational efforts and strategies are clearly mandatory, approaching not only the medical community but also the general population, perhaps by developing specific educational modules that can be implemented ~~already~~ at school level.

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AUTHOR CONTRIBUTIONS

RNTG designed the study, created the questionnaire, collected the data, and wrote the first draft. EW and RP controlled the clinical and electrophysiological data. CRB set up the CSF orexin measurements. POV designed the study, performed the statistics and revised the first draft. All authors corrected the manuscript.

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Table 1 Demographic, clinical, electrophysiological, genetic and neurochemical characteristics of the study population (n=52). Data are expressed as mean ± standard deviation.

Female sex	27 (52%)
Age at disease onset, y	22.1 ± 10.6
Age at diagnosis, y	31.4 ± 15.0
Diagnostic delay, y	8.9 ± 11.0
Body mass index, kg/m^2	26.1 ± 5.0
Epworth Sleepiness Scale	16.3 ± 4.0
Education	
- Primary school degree	13 (25%)
- Secondary school degree	22 (43%)
- College degree	5 (10%)
- University degree	11 (22%)
Work capacity at the moment of the study	
- Full	28 (54%)
- Partial	18 (35%)
- Incapacity to work	6 (11%)
Narcolepsy symptoms at the moment of diagnosis, %	
- Excessive daytime sleepiness	100
- Cataplexy	100
- Sleep paralysis	52
- Hypnagogic/hypnopompic hallucinations	48
- Fragmented night-time sleep	69
Pharmacological treatment at the moment of the study	
- Sodium oxybate	22 (42%)
- Stimulants: modafinil / methylphenidate	21 (40%) / 7 (13%)
- Antidepressants	12 (23%)
MSLT findings (n=44) at the moment of diagnosis	
- Mean sleep latency, min	2.2 ± 1.6
- Mean number of sleep onset REM periods	3.1 ± 1.0
HLA-DQB1*06:02 positivity	42 of 42 tested patients (100%)
Mean orexin level in cerebrospinal fluid, pg/ml	25 ± 41 (range: 0-163)
- No lumbar puncture	13 (25%)
- Undetectable CSF orexin levels	26 (50%)
- Reduced CSF orexin levels	13 (25%)

Table 2 Aspects that characterize the patients' troublesome journey towards the correct diagnosis of narcolepsy. Data are expressed as mean ± standard deviation (range).

Time gap between disease onset and first medical consultation	3.2±5.1y (0-29y)
The first doctor I visited was:	
- General practitioner	81%
- Neurologist	9%
- Other specialist	10%
Which person motivated the first medical consultation?	
- Patient's own initiative	56%
- Advice by another person (family, friend, teacher)	44%
Which symptom(s) urged the patient to seek medical help?	
- Excessive daytime sleepiness	71%
- Cataplexy	48%
- Hypnagogic/hypnopompic hallucinations	12%
- Sleep paralysis	6%
- Fragmented night-time sleep	25%
Number of referred physicians before correct diagnosis	3.3±1.8 (0-10)
Frequency of correct diagnosis at first medical consultation?	22%
Which specialist made the correct diagnosis?	
- General practitioner	8%
- Neurologist	82%
- Psychiatrist	2%
- Other specialist	8%
Treatment prescriptions before correct diagnosis:	
- Vitamins	27%
- Sleep extension	44%
- Antidepressants	21%
- Psychological support	21%
- Iron replacement therapy	10%
- Other	17%
What is the cause of the diagnostic delay?	
- Insufficient knowledge on narcolepsy of treating physician	64%
- Delay in seeking medical advice	24%
- Combination of the above-mentioned causes	12%

FIGURE LEGENDS

Figure 1

The histogram (A) shows the distribution of diagnostic delays among 52 patients with narcolepsy type 1. Both the diagnostic delay (B) and the interval between disease onset and first medical consultation (C) have decreased over the last decades. Grey rectangles indicate patients with >1-year interval between onset of excessive daytime sleepiness and cataplexy.

Figure 2

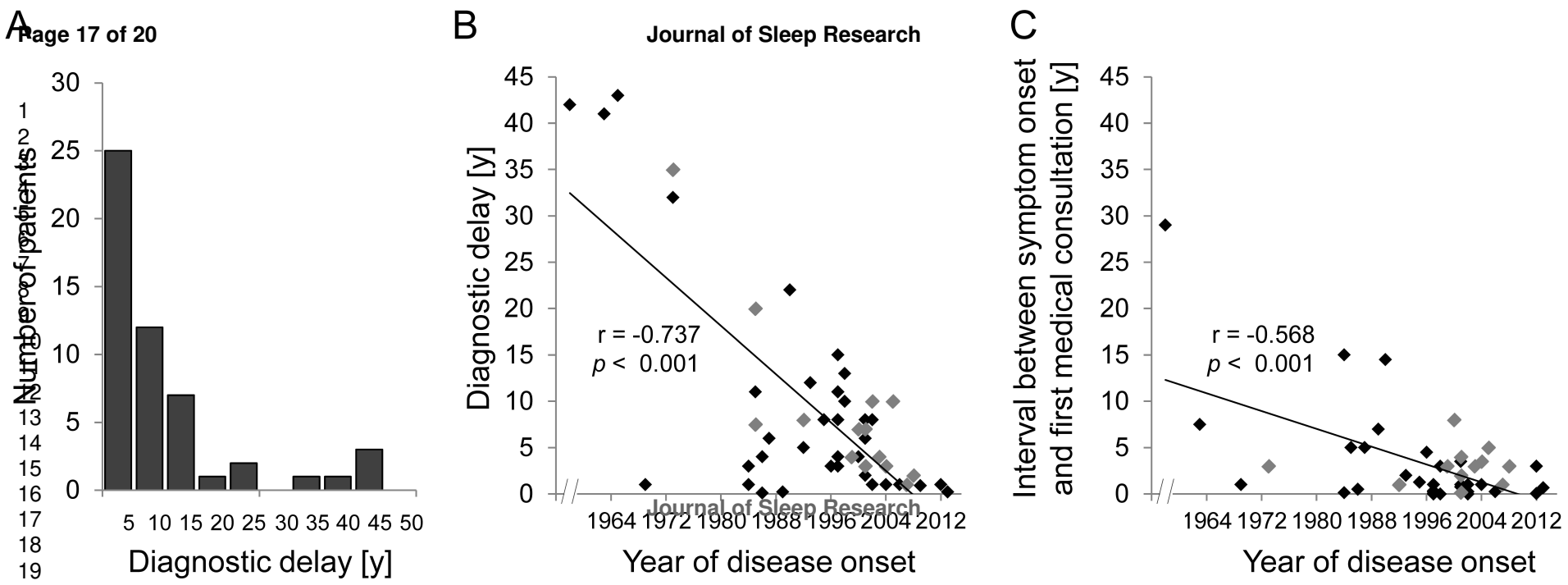
Overview on several disease-related consequences, comparing the situations before and after diagnosis (i.e. at the moment of study conduction).

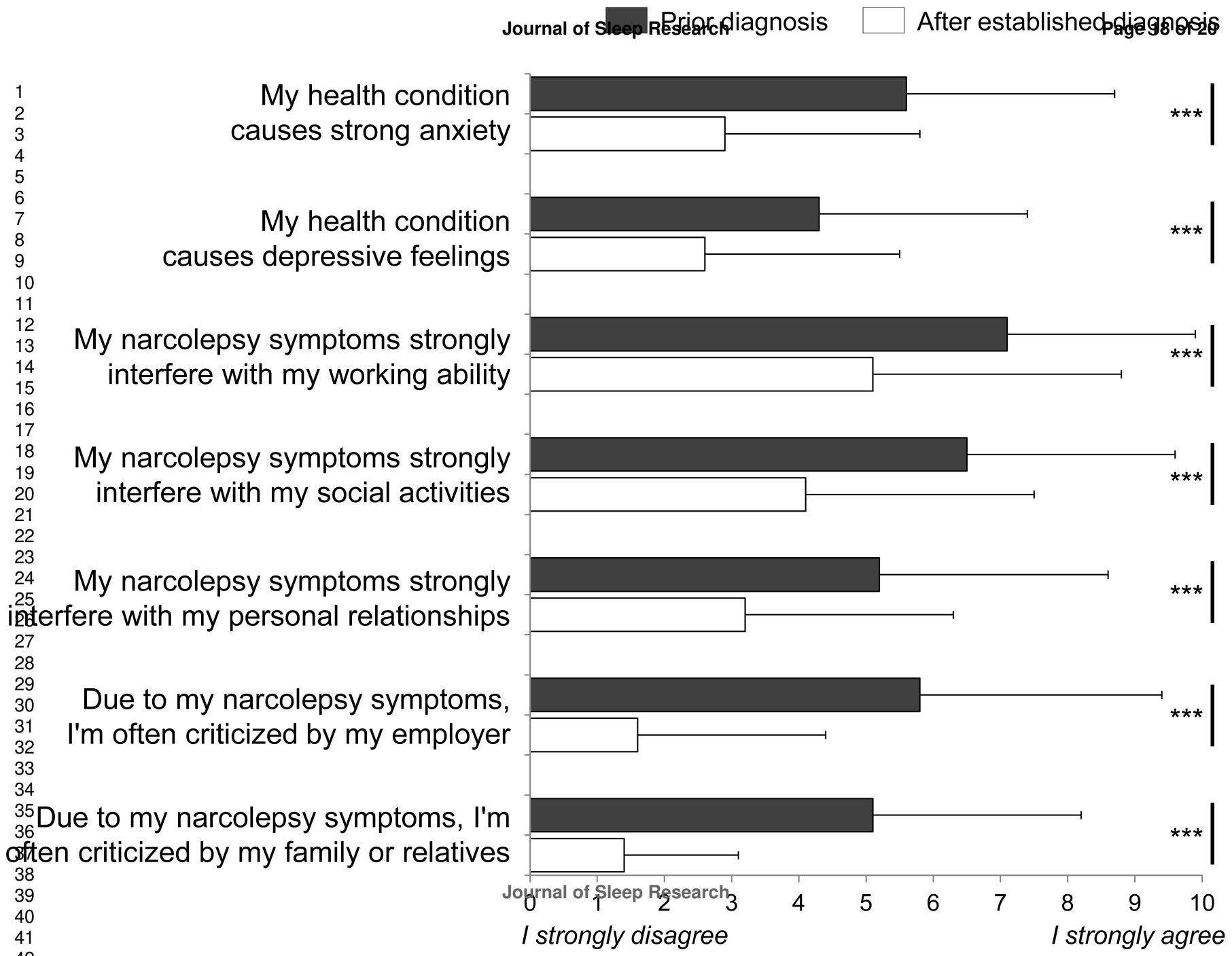
Figure 3

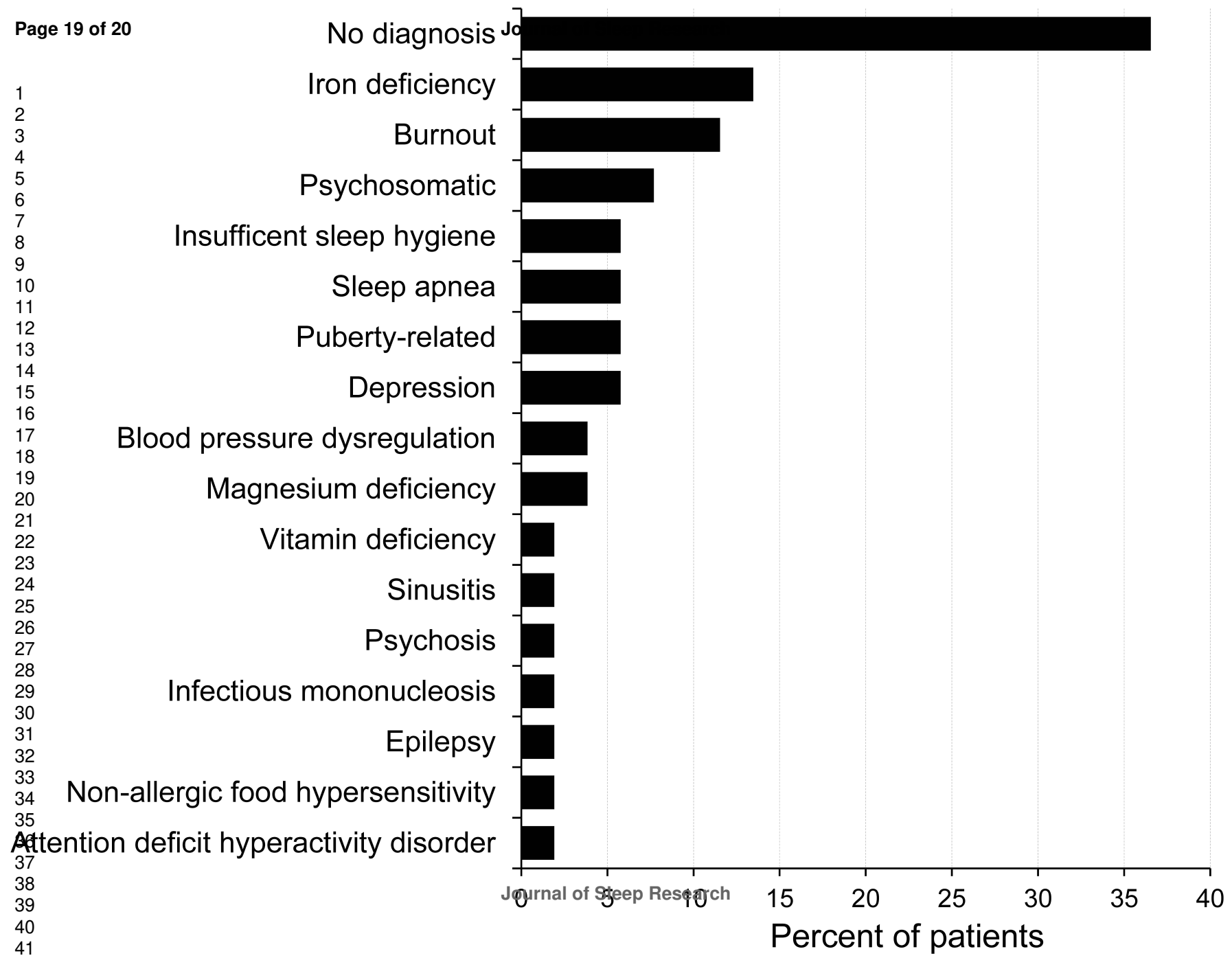
Before the correct diagnosis, patients received either no diagnosis at all or a wide variety of misdiagnoses.

Figure 4

Considerations of the narcolepsy patients about the diagnostic delay.


A
Number of patients
Diagnostic delay [y]
B
Diagnostic delay [y]
r = -0.737
p < 0.001
Year of disease onset
C
Interval between symptom onset and first medical consultation [y]
r = -0.568
p < 0.001
Year of disease onset


Prior diagnosis
After established diagnosis
My health condition causes strong anxiety
My health condition causes depressive feelings
My narcolepsy symptoms strongly interfere with my working ability
My narcolepsy symptoms strongly interfere with my social activities
My narcolepsy symptoms strongly interfere with my personal relationships
Due to my narcolepsy symptoms, I'm often criticized by my employer
Due to my narcolepsy symptoms, I'm often criticized by my family or relatives
***
0 1 2 3 4 5 6 7 8 9 10
I strongly disagree
I strongly agree


No diagnosis
Iron deficiency
Burnout
Psychosomatic
Insufficent sleep hygiene
Sleep apnea
Puberty-related
Depression
Blood pressure dysregulation
Magnesium deficiency
Vitamin deficiency
Sinusitis
Psychosis
Infectious mononucleosis
Epilepsy
Non-allergic food hypersensitivity
Attention deficit hyperactivity disorder
0
5
10
15
20
25
30
35
40
Percent of patients